UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,405	08/03/2001	Charles A. Nicolette	GZ 210300	7264

7590 10/20/2004

DEBORAH A. DUGAN,
GENZYME CORPORATION
15 PLEASANT STREET CONNECTOR
FRAMINGHAM, MA 01701-9322

EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,405	NICOLETTE, CHARLES A.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *4-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020415;20020114*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS:20020820;20021008;20030317*.

DETAILED ACTION

1. The election with traverse filed March 5, 2004 and the supplemental election with traverse filed July 1, 2004 are acknowledged and have been entered. However, because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has elected the invention of Group I, claims 1-3, drawn to a composition comprising a plurality of immunogenic ligands.

Applicant has elected the species of invention, wherein said composition comprises the immunogenic ligands of SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, and SEQ ID NO: 23.

2. The amendment filed July 1, 2004 is acknowledged and has been entered. Claims 1 and 2 have been amended. Claim 10 has been added.

3. Claims 1-10 are pending in the application. Claims 4-9 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the election filed March 5, 2004.

4. Claims 1-3 and 10, drawn to the elected invention, are currently under prosecution.

Priority

5. Applicant's claim to the benefit of the earlier filing dates of US Provisional Application Nos. 60/223,641, 60/255,502, 60/264,432, and 60/279,005 is acknowledged; however, US Provisional Application Nos. 60/223,641 and 60/255,502

do not provide an adequate written description or an enabling disclosure of the presently claimed invention for the following reason:

US Provisional Application No. 60/223,641 is deficient, as it does not teach or describe SEQ ID NOs: 13, 15, 19, 21, or 23, as set forth in the present application; and US Provisional Application No. 60/255,502 is deficient, as it does not teach or describe SEQ ID NOs: 15, 19, 21, or 23, as set forth in the present application.

Oath/Declaration

6. The declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective for the following reason:

The declaration was not executed in accordance with either 37 CFR § 1.66 or 1.68, as it was not signed or dated by the inventor.

Information Disclosure Statement

7. The information disclosures filed January 14, 2002; April 15, 2002; August 20, 2002; October 8, 2002; and March 17, 2003 have been considered. An initialed copy of each is attached hereto.

Specification

8. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible disclosure appears in the instant specification at page 8 in line 28.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable

code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference.

9. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of improperly demarcated trademark is Genbank™ at page 5 (line 26).

Appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

10. Claims 1-3 and 10 are objected to because the claims are drawn to the subject matter of a non-elected invention or species of invention.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-3 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a composition comprising the immunogenic ligand of SEQ ID NO: 9 or SEQ ID NO: 25, wherein each of said ligands is individually characterized by an ability to elicit an immune response against the

natural MART-1 peptide epitope of SEQ ID NO: 25 and the natural, full-length MART-1 polypeptide, **does not reasonably provide enablement for using** a composition comprising immunogenic ligands of SEQ ID NOs: 3, 5, 7, 11, 13, 15, 17, 19, 21, and 23, wherein each ligand is individually characterized by an ability to elicit an immune response against the same native MART-1 ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3 are drawn to a composition comprising the immunogenic ligands of SEQ ID NOs: 3, 5, 7, 11, 13, 15, 17, 19, 21, and 23, wherein each ligand is individually characterized by an ability to elicit an immune response against the native MART-1 ligand of SEQ ID NO: 25. Claim 10 is drawn to the composition of claim 1, which further comprises the immunogenic ligand of SEQ ID NO: 25 or SEQ ID NO: 9.

The teachings of the specification cannot be extrapolated to the enablement of claimed invention, because the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to use the claimed invention without having the need to perform an additional amount of undue experimentation to determine if each of the ligands of SEQ ID NOs: 3, 5, 7, 11, 13, 15, 17, 19, 21, and 23 is able to elicit an immune response against the native MART-1 ligand of SEQ ID NO: 25.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The prior art teaches a naturally occurring peptide comprising an amino acid sequence identical to the amino acid sequence set forth as SEQ ID NO: 25 in the instant application. The prior art teaches the peptide is an "epitope" of melanoma-associated tumor antigen MART-1, which binds MHC class I HLA-A2-restricted peptide

and MART-1-specific cytotoxic T cells, and is therefore capable of stimulating an immune response against itself and the native tumor antigen; see, e.g., WO 95/29193 (of record; cited by Applicant), US Patent No. 6,270,778 B1, and Guichard et al. (*J. Med. Chem.* 2000; **43**: 3803-3808). Both WO 95/29193 and US Patent No. 6,270,778 B1 also teach an analogue of the naturally occurring peptide epitope of SEQ ID NO: 25, which comprises the amino acid sequence set forth as SEQ ID NO: 9 in the instant application. The prior art teaches the peptide of SEQ ID NO: 9 binds with increased affinity to the MHC molecule, compared to the peptide of SEQ ID NO: 25. In addition, the prior teaches amino acid residues at the "anchor" and "non-anchor" positions of a peptide epitope that binds HLA-A2, which are associated with relatively "good" or "poor" binding; see, e.g., Ruppert et al. (*Cell.* 1993 Sep 10; **74** (5): 929-937) and Valmori et al. (*J. Immunol.* 1998; **161**: 6959-6962). Furthermore, the prior art teaches that there are several publicly available computer algorithms that can be used to predict which peptides and analogues will have enhanced binding affinity for MHC molecules.

The specification teaches the individual ligands of SEQ ID NOs: 3, 5, 7, 11, 13, 15, 17, 19, 21, and 23 are synthetic analogues of the naturally occurring peptide epitope of the MART-1 tumor antigen, namely the peptide epitope ("ligand") of SEQ ID NO: 25 peptides; see the specification, e.g., at page 28, lines 1-23. The specification teaches the ligands were designed with the intent of producing analogues of the ligand of SEQ ID NO: 25 that have enhanced binding affinity for the human Major Histocompatibility Complex (MHC) human leukocyte antigen (HLA)-A2 molecule; see, e.g., page 28, lines 1 and 2. The specification teaches each of the ligands of SEQ ID NOs: 3, 5, 7, 11, 13, 15, 17, 19, 21, and 23 differ from this native ligand "in that they contain mutations in the putative HLA-A2 binding domain (amino acids 1, [sic] and 2)" (page 28, lines 20-23).

The specification, however, does not show that the ligands of SEQ ID NOs: 3, 5, 7, 11, 13, 15, 17, 19, 21, and 23 have increased binding affinity, nor does the specification show these ligands are able to elicit an immune response against the native ligand of SEQ ID NO: 25 or against the native intact tumor antigen, MART-1.

The claimed invention cannot be used without the need to perform an additional amount of undue experimentation because the specification does not teach whether

each of the individual "ligands", which herein are alternatively referred to as "peptides" or "peptide epitopes", is able to elicit an immune response against the native peptide epitope of SEQ ID NO: 25 and the natural, intact MART-1 protein.

The ligands of SEQ ID NOs: 15, 17, 19, 21, and 23 differ from the ligand of SEQ ID NO: 25 at every position but the last; thus, SEQ ID NOs: 15, 17, 19, 21, and 23 are only similar to SEQ ID NO: 25 in that all have a valine residue at the carboxy-terminus. Because the ligands of SEQ ID NOs: 15, 17, 19, 21, and 23 bear no apparent substantial structural similarity to SEQ ID NO: 25, and because the art teaches that the specific immunogenicity of peptides cannot be reliably predicted, as further explained below, one skilled in the art could not use the claimed invention without first having to characterize the ligands of SEQ ID NOs: 15, 17, 19, 21, and 23 as able to elicit an immune response against the ligand of SEQ ID NO: 25 and/or the native MART-1 polypeptide.

As an aside, the results of searching relevant sequence databases using any of SEQ ID NOs: 15, 17, 19, 21, and 23 as a query fail to suggest that these sequence map to any portion of the amino acid sequence of MART-1, as do the results produced using any of SEQ ID NOs: 3, 5, 7, 9, 11, and 13 as a query. Because none of SEQ ID NOs: 15, 17, 19, 21, and 23 appear to be fragments of the amino acid sequence of MART-1, or analogues thereof, none would be reasonably expected to produce an immune response against MART-1.

On the other hand, the ligands of SEQ ID NOs: 3, 5, 7, 9, 11, and 13 are obvious analogues of SEQ ID NO: 25, as each differs from SEQ ID NO: 25 at positions 1 and 2. As noted above, the prior art teaches that the ligand of SEQ ID NO: 9 is able to elicit an immune response against itself and the intact MART-1 tumor antigen. However, the prior art does not teach or suggest altering a peptide epitope, such as that of SEQ ID NO: 25, by substituting the first and second amino acid residues with the other residues that occur in any of SEQ ID NOs: 3, 5, 7, 9, 11, and 13 to produce an analogue that has relatively enhanced binding affinity for HLA-A2. Moreover, the prior art teaches that the skilled artisan cannot reliably predict the consequences of such alterations in the amino acid sequence of the naturally occurring peptide epitope of SEQ ID NO: 25.

Guichard et al. (cited *supra*), for example, teaches they and others were surprised to discover that in the case of the MART-1 peptide epitope of SEQ ID NO: 25, which maps to amino acids 27-35 of the native MART-1 antigen, the substitution of alanine by leucine or methionine at the second position ("P2"), although considerably improving binding to HLA-A2, resulted in a dramatic reduction of the peptide's ability to stimulate an immune response (paragraph bridging pages 3803 and 3804).

In general, the art of synthesizing functional equivalents of naturally occurring proteins is very unpredictable in nature, since, for example, Bowie et al. (*Science*. 1990 Mar 16; **247** (4948): 1306-1310) teaches the skilled artisan cannot reliably predict which variants of a native protein function similarly to the native protein, and which do not, because the prediction of a protein's propensity to form a particular structure, and to subsequently infer detailed aspects of function from the predicted structure, is extremely complex; see entire document (e.g., page 1306, column 1). Furthermore, Bowie et al. teaches, while it is known that many amino acid substitutions are possible in any given protein, and proteins are surprisingly tolerant of amino acid substitutions, the positions within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited, particularly at positions where the amino acid residues have critical roles in the protein's structure and function, and these regions can tolerate only conservative substitutions, or none at all (page 1306, column 2).

Although Schirle et al. (*J. Immunol. Methods.* 2001; **257**: 1-16), for example, teaches that several computer algorithms are now available for use in predicting the structures of synthetic peptides that bind MHC molecules, Schirle et al. teaches, "the identified epitopes still have to pass the ultimate test: they have to prove to be useful in the in vivo situation" (page 11, paragraph bridging columns 1 and 2).

Moreover, Anderson et al. (*Tissue Antigens*. 2000 Jun; **55** (6): 519-531) teaches there is poor correspondence between predicted and experimental binding of peptides to class I MHC molecules; see entire document (e.g., the abstract). Andersen et al. teaches, while knowledge of the peptide binding motifs of individual class I MHC molecules permits the selection of potential peptide antigens, there is no strong

correlation between actual and predicted binding when using predictive computer algorithms, and therefore the peptide binding assay remains an important step in the identification of cytotoxic T lymphocyte (CTL) epitopes, which cannot be substituted by predictive algorithms (abstract).

Furthermore, Feltkamp et al. (*Mol. Immunol.* 1994 Dec; **31** (18): 1391-1401) teaches, while efficient binding of peptide epitopes to MHC class I molecules is required to elicit an immune response against the peptide epitope or the intact antigen, an increased binding affinity does not consistently and reproducibly relate to a peptide epitope's immunogenicity, i.e., its ability to elicit a peptide- and antigen-specific immune response; see entire document (e.g., the abstract). Feltkamp et al. teaches that other factors, in addition to its binding affinity for an MHC molecule, determine whether a peptide epitope, or analogue thereof, will be able to stimulate an effective immune response; see, e.g., the abstract.

van der Burg et al. (*J. Immunol.* 1996 May 1; **156** (9): 3308-3314) teaches that the immunogenicity of peptides bound to MHC class I molecules depends on the stability of the complex, not just the binding affinity; see entire document (e.g., the abstract). Moreover, van der Burg et al. teaches that the immunogenicity of peptide epitopes can be more accurately predicted by their dissociation rate, as opposed to the MHC class I binding affinity; see, e.g., the abstract.

Thus, even if each of the individual peptides of the claimed invention were to have greater HLA-A2 binding affinity than the naturally occurring peptide epitope of SEQ ID NO: 25, the invention could be still not be used to stimulate an immune response against the peptide of SEQ ID NO: 25 or against the native MART-1 polypeptide without first performing an undue amount of experimentation, since it would still be necessary to determine if the analogues are capable of stimulating an immune response against the native protein or it natural peptide epitope of SEQ ID NO: 25.

As such, it is noted that Valmori et al. (*Journal of Immunology*. 1998; **160**: 1750-1758), for example, teaches analogues of SEQ ID NO: 25 that bound more efficiently than the natural peptide epitope, but which were poorly recognized by tumor reactive cytotoxic T lymphocytes (CTL); see entire document (e.g., the abstract). Because the

analogues were poorly recognized by antigen-specific CTL, the analogues could not effectively elicit an immune response against the native MART-1 antigen, or against tumor cells expressing the antigen.

Finally, it is noted that the specification asserts the claimed invention can be used therapeutically. The objective of using the claimed composition therapeutically would be to stimulate the proliferation of cytotoxic T cells (CTL) that are reactive against melanoma cells, for example, which express MART-1. However, Boon (*Advances in Cancer Research*, 1992, **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden; see entire document (e.g., page 206, paragraph 2). Boon teaches the establishment of immune tolerance may therefore have already occurred in the patient; and in such cases, active specific immunization will be fruitless, since anergic CTL cannot be activated, will not proliferate, and are deficient in effector function (page 206, paragraph 2). Thus, while a ligand might stimulate an effective immune response in one patient having a low tumor burden, perhaps, it is entirely possible that the ligand will not be immunogenic in another. Accordingly, the skilled artisan cannot predict whether each of the peptide analogues of which the claimed composition is composed will individually elicit an immune response against the native epitope or antigen in a patient carrying a large tumor burden; and therefore, the skilled artisan could not use the claimed invention without having to first perform an undue amount of additional experimentation to determine if the analogues are each capable of doing so.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the preponderance of factual evidence of record indicates the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation to determine if each of the individual ligands of which the claimed composition are able to stimulate an effective

immune response against the native ligand of SEQ ID NO: 25 or the native, intact MART-1 tumor antigen.

Conclusion

13. No claims are allowed.

14. Claims 1-3 and 10, drawn to the elected invention, are free of the prior art of record because the prior art of record does not teach or fairly suggest the peptides of SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, or SEQ ID NO: 23.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
September 20, 2004